of Claims 1-6 and 15-23 as amended herein is attached for the Examiner's convenience as Appendix C. Applicants gratefully acknowledge a telephone interview with the Examiner and Applicants' undersigned representative on October 23, 2001 to discuss the present rejections.

The Office Action stated that the application did not comply with the sequence listing rules because there were sequences on page 44 and sequences in Figures 5A and 5B that were not listed. Applicants have submitted herewith an amended Sequence Listing which contains those sequences and a Statement Under 37 C.F.R. § 1.821(f). Applicants have also amended pages 15 and 44 of the specification to include SEQ ID NOs.

The Office Action objected to claim 15 as being in improper form because a multiple dependent claim cannot properly depend from another multiple dependent claim. Claim 15 has been amended so that it is multiply dependent on claims 1-3. None of claims 1-3 is a multiple dependent claim. Therefore, Applicants submit that the objection to claim 15 has been overcome, and Applicants request consideration of claim 15.

Claims 1-6 and 16-23 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner acknowledged that the claims were enabled for BPI protein of SEQ ID NO: 1. However, it was the Examiner's position that the specification does not reasonably provide enablement for any BPI analog or variant. Claims 1-6 and 16-23 were also rejected under 35 U.S.C. § 112, second paragraph, as indefinite. It was the Examiner's position that, given the myriad of BPI protein activities, the metes and bounds of which of these activities should define what is and is not BPI protein are vague and indefinite. Applicants respectfully disagree and assert that the claims are fully enabled and definite for the reasons outlined below.

As described in detail in the specification, BPI proteins have been demonstrated to have a great variety of activities and uses. Indeed, BPI proteins are remarkable in having a

multiplicity of activities (see, for example, specification at pages 1-10, including page 9, lines 14-17 and page 10, lines 22-29). As described in detail in the specification, a variety of BPI proteins have been produced with one or more of these activities, including biologically active synthetic and recombinant proteins, fragments, variants, analogs and peptides (see, for example, specification including at pages 16-19).

In order to provide additional clarity within the present claims, Applicants have amended claims 1-6 and 16-23 so that they recite specific activities (antimicrobial, lipopolysaccharide-binding, and heparin-binding activities) that characterize and define a BPI protein within the present claims. A BPI protein within the claims may have additional activities as well, and Applicants reserve the right to identify a BPI protein by other activities in other claims filed in one or more continuing applications or in unrelated applications.

The Examiner has asserted that "a protein which is an analog or variant or a fragment of BPI cannot be determined as to whether it is properly a BPI protein without an activity assay" and that "the assaying of protein activity for BPI activity is deemed essential subject matter." Applicants respectfully submit that assays for antimicrobial, lipopolysaccharide-binding, and heparin-binding activities are well-known in the art generally and well-known for the art for BPI proteins specifically. In addition, the specification describes and incorporates by reference a number of U.S. patents that describe numerous assays for such activities. For example, U.S. Patent No. 5,523,288 (incorporated by reference at page 6, line 32 and page 7) includes Examples 1-4 and describes assays to determine antimicrobial activity with BPI protein products; U.S. Patent No. 5,643,875 (incorporated by reference at page 5, lines 18-21) includes Example 1 which describes a study designed to investigate the lipopolysaccharide-binding and neutralizing activities of BPI protein products in humans rendered endotoxemic by intravenous infusion of bacterial lipopolysaccharide (also referred to as endotoxin); and U.S. Patent No. 5,348,942 (incorporated by reference at page 7, lines 6

and 10-12) includes Examples 1, 3-5, and 12 and describes assays to determine heparin-binding and neutralizing activity with BPI protein products.

The rejection of claim 4 as vague and indefinite because that claim referred to Table 31, has been mooted by Applicants' amendment to correct a typographical error. Claim 4 now refers to Table 3. The rejection of claim 22 as vague and indefinite because that claim referred to Figures 2-20 has been mooted by Applicants' amendment to correct this typographical error. Claim 22 now refers to Figures 5A-5B and Table 4.

Claims 1-6 were additionally rejected under 35 U.S.C. § 101. It was the Examiner's position that the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. Applicants respectfully disagree and submit that each of original claims 1-6 had set forth a positive step. Each of those claims require one to model a BPI protein or a BPI-related lipid transfer protein. Because those claims set forth a step, they are distinguishable from the claims at issue in Ex parte Dunki and Clinical Products Limited v. Brenner. Original claims 1-6 were more analogous to the claims in *Ex parte Bouillon,* 1998 WL 1744151 (Bd. Pat. App. & Interf. 1998) (unpub.). In *Bouillon,* the Board reversed the rejection of claim 21 under 35 U.S.C. § 101, noting "Although claim 21 does not use the term 'process' or 'method', it does recite a skin cleaning process involving a step of applying a novel skin cleansing agent and water to the skin. This applying step is not 'an intended use' step as alleged by the examiner. Rather, it is a positive step." *Id.,* at *2. Similarly, original claims 1-6 recited a positive step. Nonetheless, in order to expedite prosecution, Applicants have amended the claims to recite a "method" rather than a "use".

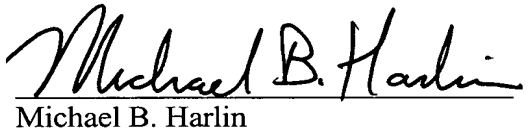
Applicants respectfully submit that the rejections to claims 1-6 and 16-23 under § 112 and § 101 as well as the objection to claim 15 may properly be withdrawn in view of the amendments and remarks herein.

The Commissioner is hereby authorized to charge Account no. 13-0017 (McAndrews, Held & Malloy) for any fee deficiency, or credit any overpayment associated with this application.

In view of the foregoing amendments and remarks, Applicants submit that a complete response has been made to the Office Action and that the claims as amended herein are in condition for allowance. The Examiner is invited to telephone Applicants' undersigned representative if the Examiner believes, for any reason, that personal communication would expedite prosecution of this application.

Respectfully submitted,

Dated: October 24, 2001



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Appendix A
Changes Made to The Specification
(Deletions in brackets, additions underlined)

Page 15, lines 3-28:

Figs. 5 (A) and 5 (B) The amino acid sequences of human BPI **(SEQ ID NO: 3)**, LBP **(SEQ ID NO: 4)**, PLTP **(SEQ ID NO: 5)**, and CETP **(SEQ ID NO: 6)**. The alignment was performed with CLUSTAL [D. G. Higgins and P. M. Sharp, Gene, 73:237 (1989)] using all eleven known protein sequences from mammals [R. R. Schuman, et al., Science, 249:1429 (1990); D. Drayna et al., Nature, 327:632 (1987); R. Day et al., J. Biol. Chem., 269:9388 (1994); S. R. Leong and T. Camerato, Nucleic Acids Res., 18:3052 (1990); M. Nagashima, J. W. McLean, R. M. Lawn, J. Lipid Res., 29:1643 (1988); M. E. Pape, E. F. Rehber, K. R. Marotti, G. W. Melchior, Artheriosclerosis 11:1759 (1991); G. Su et al., J. Immunol., 153:743 (1994); P. W. Gray et al., J. Biol. Chem. 264: 9505 (1989); Albers et al., Biochem. Biophys. Acta, 1258:27 (1995); X. C. Jiang et al., Biochemistry, 34:7258 (1995); L. B. Agellon et al., Biochemistry, 29:1372 (1990); X. C. Jiang et al., J. Biol. Chem., 266:4631 (1991)] but only the four human sequences are shown. Residues that are completely conserved in all proteins are indicated below the sequence *; those which are highly conserved are indicated by •. The secondary structure of BPI is indicated above the sequences. The strands are indicated by arrows; strands which make up the central β sheet are shown with gray arrows. Because of the β bulges and pronounced twisting, some of the β strands have one or more residues that do not show classical H-bonding patterns or ΦΨ angles; these breaks are indicated by ^ above the strands. The α helices are shown as cylinders, and one-residue breaks in helices B and B' are indicated with a vertical dashed line. The horizontal dashed line indicates the linker region. Peptides from BPI and LBP with the highest lipopolysaccharide-binding activity (Little, et al., J. Biol. Chem. 268: 1865 (1994); Taylor et al., J. Biol. Chem. 270: 17934 (1995)) are in bold italics. The disulfide bond is indicated by S-S. Residues with atoms within 4 Å of the NH_2 -terminal lipid are highlighted with gray

shading; residues within 4 Å of the COOH-terminal lipid are shown with white letters in black boxes.

Page 44, lines 8-24:

The glycosylation site was next removed by replacing the region from a unique XcmI site to a unique SphI site within the BPI gene in pSS101 with an annealed oligonucleotide that contained the codon (TCC) for the serine at amino acid position 351 changed to the codon (GCC) for alanine as shown below.

```
Wild type
      XcmI                                          SphI
...CCC AAC TCC TCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC (SEQ ID NO:7)
...GGG TTC AGG AGG GAC CGA AGG GAG AAG GAC TAA CCG TAC GTG (SEQ ID NO:8)
   Pro Asn Ser Ser Leu Ala Ser Leu Phe Leu Ile Gly Met His (SEQ ID NO:9)
               351
Nonglycosylated
        XcmI                                        SphI
...CCC AAC TCC GCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC (SEQ ID NO:10)
...GGG TTC AGG CGG GAC CGA AGG GAG AAG GAC TAA CCG TAC GTG (SEQ ID NO:11)
   Pro Asn Ser Ala Leu Ala Ser Leu Phe Leu Ile Gly Met His (SEQ ID NO:12)
               351
```

This step generated the plasmid pSS102.

Appendix B
Changes Made to Claims 1-6 and 16-23
(Deletions in brackets, additions underlined)

1. **A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using** **[Use of]** atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to model **[a]** **the** BPI protein.

2. **A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") related lipid transfer protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using** **[Use of]** atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to model **[a]** **the** BPI-related lipid transfer protein.

3. The **method [use]** according to claim 2, wherein the BPI-related lipid transfer protein is lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

4. The **method [use]** according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in **Table 3** **[Table 31]**.

5. The **method [use]** according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI **of SEQ ID NO: 2**.

6. The **method [use]** according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI **of SEQ ID NO: 2**.

15. The **method [use]** according to any of claims 1 – **3 [14]**, wherein said atomic coordinates are according to Table 4.

16. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein **having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method** comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI protein suitable for visualization and further computational manipulation.

17. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI")-related lipid transfer protein **having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method** comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI-related lipid transfer protein suitable for visualization and further computational manipulation.

18. The **method [use]** according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3.

19. The **method [use]** according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI **of SEQ ID NO: 2**.

20. The **method [use]** according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about

54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI **of SEQ ID NO: 2**.

21. A method for providing an atomic model of a BPI protein, or fragment, analog or variant thereof, **having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method** comprising

(a) providing a computer readable medium having stored thereon atomic coordinate/x-ray diffraction data of the BPI protein, or fragment, analog or variant thereof, in crystalline form, the data sufficient to model the three-dimensional structure of the BPI protein, or fragment, analog or variant thereof;

(b) analyzing, on a computer using at least one subroutine executed in said computer, atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing algorithm selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) obtaining atomic coordinate data defining the three-dimensional structure of at least one of said BPI protein, or fragment, analog or variant thereof.

22. A method according to claim 21, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or an amino acid sequence data comprising at least one structural domain or functional domain of a BPI, LBP, CETP or PLTP corresponding to at least one BPI or mutant primary sequence of Figures 2-20 or Table 2, or a fragment thereof; and wherein said analyzing step further comprises analyzing said sequence data.

23. A computer-based system for providing atomic model data of the three-dimensional structure of BPI protein, or fragment, analog or variant thereof, a BPI mutant or a BPI fragment, **having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the system** comprising the following elements:

(a) at least one computer readable medium (CRM) having stored thereon atomic coordinate/x-ray diffraction data of said BPI protein, or fragment, analog or variant thereof;

(b) at least one computing subroutine that, when executed in a computer, causes the computer to analyze atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) retrieval means for obtaining atomic coordinate output data substantially defining the three-dimensional structure of said BPI protein, or fragment, analog or variant thereof.

Appendix C
Specie A Claims 1-6 and 15-23
of U.S. Application No. 09/446,415

1. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to model the BPI protein.

2. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") related lipid transfer protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the step of using atomic coordinates of bactericidal/permeability-increasing ("BPI") protein, or fragment, analog or variant thereof, to model the BPI-related lipid transfer protein.

3. The method according to claim 2, wherein the BPI-related lipid transfer protein is lipopolysaccharide-binding protein (LBP), cholesteryl ester transferase protein (CETP) or phospholipid transfer protein (PLTP), or fragment, analog or variant thereof.

4. The method according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3.

5. The method according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

6. The method according to any of claims 1-3, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84

to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

15. The method according to any of claims 1 – 3, wherein said atomic coordinates are according to Table 4.

16. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI") protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI protein suitable for visualization and further computational manipulation.

17. A method of three-dimensional modeling of a bactericidal/permeability-increasing ("BPI")-related lipid transfer protein having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising the steps of:

(a) providing three-dimensional atomic coordinates derived from X-ray diffraction measurements of a BPI protein in a computer readable format;

(b) inputting the data from step (a) into a computer with appropriate software programs;

(c) generating a three-dimensional structural representation of the BPI-related lipid transfer protein suitable for visualization and further computational manipulation.

18. The method according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3.

19. The method according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by at least one amino acid sequence,

or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

20. The method according to any of claims 16-17, wherein the BPI protein comprises a binding site characterized by amino acid residues of at least one binding pocket as defined in Table 3 and a binding site characterized by at least one amino acid sequence, or variant of the sequence, selected from positions about 17 to about 45, positions about 36 to about 54, positions about 65 to about 99, positions about 84 to about 109, positions about 142 to about 164, or positions about 142 to about 169 of BPI of SEQ ID NO: 2.

21. A method for providing an atomic model of a BPI protein, or fragment, analog or variant thereof, having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the method comprising

(a) providing a computer readable medium having stored thereon atomic coordinate/x-ray diffraction data of the BPI protein, or fragment, analog or variant thereof, in crystalline form, the data sufficient to model the three-dimensional structure of the BPI protein, or fragment, analog or variant thereof;

(b) analyzing, on a computer using at least one subroutine executed in said computer, atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing algorithm selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) obtaining atomic coordinate data defining the three-dimensional structure of at least one of said BPI protein, or fragment, analog or variant thereof.

22. A method according to claim 21, wherein said computer readable medium further has stored thereon data corresponding to a nucleic acid sequence or

an amino acid sequence data comprising at least one structural domain or functional domain of a BPI, LBP, CETP or PLTP corresponding to at least one BPI or mutant primary sequence of Figures 2-20 or Table 2, or a fragment thereof; and wherein said analyzing step further comprises analyzing said sequence data.

23. A computer-based system for providing atomic model data of the three-dimensional structure of BPI protein, or fragment, analog or variant thereof, a BPI mutant or a BPI fragment, having antimicrobial, lipopolysaccharide-binding, and heparin-binding activities, the system comprising the following elements:

(a) at least one computer readable medium (CRM) having stored thereon atomic coordinate/x-ray diffraction data of said BPI protein, or fragment, analog or variant thereof;

(b) at least one computing subroutine that, when executed in a computer, causes the computer to analyze atomic coordinate/x-ray diffraction data from (a) to provide atomic coordinate data output defining an atomic model of said BPI protein, or fragment, analog or variant thereof, said analyzing utilizing at least one computing subroutine selected from the group consisting of data processing and reduction, auto-indexing, intensity scaling, intensity merging, amplitude conversion, truncation, molecular replacement, molecular alignment, molecular refinement, electron density map calculation, electron density modification, electron map visualization, model building, rigid body refinement, positional refinement; and

(c) retrieval means for obtaining atomic coordinate output data substantially defining the three-dimensional structure of said BPI protein, or fragment, analog or variant thereof.